REMARKS

Upon entry of this amendment, claims 14 and 36-54 are pending in the instant application. Claims 1-13 and 15-35 are cancelled herein. Applicant reserves the right to prosecute the cancelled subject matter, as well as the originally presented claims, in continuing applications. Claim 14 has been amended herein and new claims 36-54 have been added.

Support for the claim amendments presented herein is found throughout the specification and in the claims as originally filed. For example, support for the transporter peptides recited in amended claim 14 and new claims 36-44 is found at least at pg. 23, lines 20-25; at pg. 24, lines 3-5; at pg. 24, lines 10-15; at pg. 24, lines 19-20; and at pg. 25, lines 3-5. Support for the transporter peptides recited by new dependent claims 45-48 is found at least at pg. 3, lines 26-27; pg. 10, lines 24-26; pg. 17, lines 20-22; pg. 19, lines 7-8; pg. 19, lines 16-17; and pg. 19, lines 23-25. In addition, support for the methods of contacting cells recited by new dependent claims 49-53 is found at least at pg. 12, lines 13-16; at pg. 13, lines 4-6; and at pg. 13, lines 12-14. Finally, support for the methods of detecting translocation recited by new claims 54-58 is found at least at pg. 9, lines 20-25; at pg. 11, lines 22-26; at pg.16, lines 20-21; at pg.16, lines 20-27; at pg. 16, line 31 through pg. 17, line 5; at pg. 20, lines 13 – 32; and at pg. 24, lines 19 - 20.

Accordingly, no new matter has been added by these amendments.

I. PRIORITY

The Examiner has indicated that the specification does not contain a specific reference to the provisional application to which the instant application claims priority. Applicant notes that the specification has been amended to recite that the instant application "claims priority to U.S. Provisional Patent Application No. 60/240,315, filed on October 13, 2000", in accordance with 35 U.S.C. § 119(e), 37 C.F.R. §1.78(a)(5) and MPEP 202.01. Accordingly, Applicant requests that the Examiner withdraw this objection.

II. ELECTION / RESTRICTIONS

The Examiner has acknowledged Applicant's election without traverse of Group IV (*i.e.*, claim 14) in Paper No. 11 filed on July 15, 2003. Applicant has cancelled the claims drawn to

non-elected inventions (*i.e.*, claims 1 – 13 and 15 – 35) and reserves the right to pursue the cancelled subject matter, as well as the original claims, in continuing applications.

III. INFORMATION DISCLOSURE STATEMENT

The Examiner has indicated that the listing of references in the specification is not a proper Information Disclosure Statement. Applicant notes that all but one of the references presented on pgs. 26-31 of the as-filed specification were cited in an Information Disclosure Statement filed on February 14, 2002 in accordance with 37 C.F.R. §§1.97-1.98. In the Office Action mailed September 30, 2003, the Examiner considered and initialed each of the cited references. In addition, Applicant is filing a Supplemental Information Disclosure Statement herewith that cites the last reference. Applicant, therefore, believes all of the references listed on pgs. 26-31 of the specification have been properly disclosed in accordance with 37 C.F.R. §§ 1.97 and 1.98.

IV. CLAIM OBJECTIONS

The Examiner has objected to claim 14 as being dependent on a non-elected independent claim (*i.e.*, claim 1). Amended claim 14 has been rewritten as an independent claim and, therefore, does not depend on a non-elected claim. Accordingly, Applicant requests that the Examiner withdraw this objection.

V. CLAIM REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected claim 14 under 35 U.S.C. §112, first paragraph for lack of written description. First, the Examiner asserts that "[t]he specification does not disclose the method of translocating a transporter peptide across the membrane of pancreatic B-cells." Office Action pg. 4. The claims have been amended to address the Examiner's rejection.

Claim 14 now recites a method of translocating a transporter peptide into a pancreatic B-cell, involving contacting a pancreatic B-cell with a transporter peptide having the amino acid sequence $X_mRX_oRX_n$, wherein X is a non-basic amino acid; m is an integer from zero to fourteen; n is an integer, independent of m, between zero and fourteen; and o is an integer, independent of m and n, between zero and five, for a time and under conditions sufficient to allow a transporter peptide to translocate across a membrane of the B-cell.

Applicant contends that the method of amended claim 14 is recited in the specification. For contacting a B-cell *in vitro*, the specification as-filed discloses a method whereby transporter peptides are "...incubated with cells at a temperature which enables active metabolism of the cells" or that the transporter peptide can be "...injected into particular cells." (*See* specification at pg. 10, lines 29-32). The specification also discloses a method whereby phage-bearing, randomized peptide sequences were added to B-cell cultures and allowed to incubate. During incubation, phage-bearing peptides contacted B-cells resulting in the translocation across a B-cell membrane and enrichment of particular phage-bearing peptides. After several cycles of contact and enrichment, the peptides were characterized. As shown in Table 2, the phage-bearing transporter peptides of SEQ ID NOs: 1, 2 and 3 translocated a B-cell membrane by this method. (*See* specification at pg. 27, lines 20-25).

Additionally, the specification as-filed provides specific examples of methods of translocating a B-cell membrane with transporter peptides. In particular, the specification discloses a time-sequence titration experiment documenting the time-dependent, increased translocation of the phage-bearing transporter peptide of SEQ ID NO:1 across a B-cell membrane by use of this method. (*See* specification at pg. 24, lines 1-5). Additionally, the specification describes cell specificity experiments in which phage-bearing transporter peptides of SEQ ID NO:1 translocated across a B-cell membrane, by use of this method, 10,000- to 100,000-fold more efficiently than the same peptides translocated across other cell membranes. (*See* specification at pg. 24, lines 10-15). The specification also describes a method of translocating a B-cell membrane by contacting B-cells with detectably-labeled transporter peptides. More specifically, the method involved contacting B-cells with a FITC-labeled peptides by incubation. After incubation, fluorescence microscopy revealed that the transporter peptide with SEQ NO:1 translocated a B-cell membrane in an amount sufficient to create a signal, whereas the same transporter peptide contacting other cell types did not translocate the cell membrane in an amount sufficient to generate a signal. Consequently, Applicant asserts that the specification as-filed provides disclosure of methods of translocating a transporter peptide across a B-cell membrane as recited in amended claim 14.

Second, the Examiner asserts that "[t]he specification disclosure does not disclose the use of peptides with SEQ ID NOs: 2-6 in the claimed method." Office Action pg. 4. The claims

have been amended to address the Examiner's rejection. As previously discussed, the claims have been amended herein to recite a method of translocating a transporter peptide of amino acid sequence $X_mRX_oRX_n$ across a B-cell membrane by contacting a B-cell with a transporter peptide. Applicant notes that SEQ ID NOs: 1, 2, 3 and 6 conform to the amino acid sequence $X_mRX_oRX_n$, and that claim 14 (as amended) no longer encompasses SEQ ID NOs: 4 and 5. Additionally, the specification as-filed describes a method of translocating a B-cell membrane with transporter peptides of SEQ ID NOs: 1, 2, 3 and 6 by contacting B-cells with a library of phage-bearing transporter peptides to identify phage-bearing transporter peptides which are able to translocate a B-cell membrane. In this example, transporter peptides of SEQ ID NOs: 1, 2, 3 and 6 translocated a B-cell membrane by the disclosed method of contacting B-cells with the transporter peptides. Despite the competition of $3x10^8$ independent phages, at the end of three rounds of selection and enrichment, 85% of the transporter peptides translocating a B-cell membrane by the method of amended claim 14 had sequences of SEQ ID NOs: 1, 2 or 3. (*See* specification at pg. 27, lines 20-25). At the final cycle of enrichment, phage-bearing transporter peptides of SEQ ID NOs: 1, 2, 3 and 6 had translocated a B-cell membrane by the method of amended claim 14. Consequently, Applicant asserts that the specification-as-filed discloses the use of transporter peptides with SEQ ID NOs: 1, 2, 3 and 6 in the claimed method.

Third, the Examiner asserts that "the invention lacks showing of sufficient identifying characteristics or lacks examples of the transporter peptides of SEQ ID NOs 2-6 in the claimed method to demonstrate possession of the claimed generic[sic]." Office Action pg. 4. The claims have been amended to address the Examiner's rejection. As previously discussed, the claims have been amended herein to recite a method of translocating a transporter peptide of amino acid sequence $X_mRX_oRX_n$ across a B-cell membrane by contacting a B-cell with the transporter peptide. Applicant contends that the specification discloses sufficient identifying characteristics to demonstrate possession of the claimed genus.

Most broadly, the specification as-filed provides general physical and functional characteristics of these transporter peptides. As described in the specification, *e.g.*, at page 9, line 4 and at page 16, lines 1-2, the transporter peptides of the claimed invention include a "consensus internalization motif", $X_mRX_oRX_n$, which directs "efficient and specific intracellular delivery" of the transporter peptides to B-cells in the βTC-3 cell model. More specifically, the

specification identifies four transporter peptides (*i.e.*, SEQ ID NOs: 1, 2, 3 and 6) conforming to the "consensus internalization motif", $X_mRX_oRX_n$ that translocate a B-cell membrane by the method of amended claim 14.

Additionally, the specification also describes methods for identifying, purifying and sequencing other transporter peptides containing the "consensus internalization motif", $X_mRX_oRX_n$, that are able to translocate a B-cell membrane. (*See e.g.*, specification in Example 2 at pg. 21, lines 17-29 and in Example 3 at pg. 23, line 7 through pg. 24, line 15). Consequently, the specification discloses a general structure and function, discloses specific examples of transporter peptides with that structure and function, and discloses a method to identify additional transporter peptides for use in the claimed method. Applicant contends that the specification discloses sufficient identifying characteristics to demonstrate possession of the claimed genus of peptides.

Applicant also contends that the specification discloses a sufficient number of examples of the transporter peptides of SEQ ID NOs: 1, 2, 3 and 6 to demonstrate possession of the claimed genus. As previously mentioned, claim 14 has been amended to recite a method of translocating a transporter peptide of amino acid sequence $X_mRX_oRX_n$ across a B-cell membrane by contacting a B-cell with the transporter peptide. Phage-bearing peptides contacted B-cells resulting in the translocation across a B-cell membrane and enrichment of particular phage-bearing peptides. After several cycles of contact and enrichment, the peptides were characterized. Despite the competition of $3x10^8$ independent phages, at the end of three rounds of selection and enrichment, 85% of the transporter peptides translocating a B-cell membrane by the method of claim 14 as-amended had sequences of SEQ ID NOs: 1, 2 or 3. (*See* specification at pg. 27, lines 20-25) At the final cycle of enrichment, phage-bearing transporter peptides of SEQ ID NOs: 1, 2, 3 and 6 had translocated a B-cell membrane by the method of amended claim 14. As a result, Applicant contends that the specification provides identifying characteristics and sufficient examples of transporter peptides of the claimed invention to demonstrate possession of the claimed transporter peptides.

Finally, the Examiner asserts that "the sequences with SEQ ID NOs: 4 and 5 do not share or have the required convertase consensus RXXR, such that the assertion of that the peptides with SEQ ID NOS 4 and 5 are also transporter peptides [sic] ." As discussed above, Applicant

notes that claim 14 has been amended to recite a method of translocating a transporter peptide of amino acid sequence $X_mRX_oRX_n$ across a B-cell membrane by contacting a B-cell with the transporter peptide. Claim 14 as amended no longer encompasses the peptides of SEQ NOs: 4 and 5. Additionally, the physical and functional characteristic of interest in the claimed method is the "consensus internalization motif", $X_mRX_oRX_n$, which directs "efficient and specific intracellular delivery" of the transporter peptides to B-cells in the βTC-3 cell model. The transporter peptides of SEQ ID NOs: 1, 2, 3 and 6 share this consensus motif and the specification discloses the use of these transporter peptides in the claimed method. Consequently, the amended claims render the Examiner's concerns moot.

As a result, Applicant contends that the specification as filed describes methods of translocating a B-cell by contacting a B-cell membrane with a transporter peptide. Applicant further contends that this description describes identifying characteristics and provides examples of the transporter peptides used in the claimed method to demonstrate possession of the claimed genus. As a result, Applicant requests that the Examiner withdraw this rejection.

Applicant also notes that claim 50 has been added. New claim 50 (and its dependent claims) recites a method of detecting the translocation of a transporter peptide across a membrane of a pancreatic B-cell by contacting a population of B-cells with a transporter peptide with the sequence $X_mRX_oRX_n$, wherein X is a non-basic amino acid; m is an integer from zero to fourteen; n is an integer, independent of m, between zero and fourteen; and o is an integer, independent of m and n, between zero and five, incubating the B-cells and transporter peptide for a time and under conditions sufficient to enable penetration into the cells; and detecting whether the transporter peptide is present inside the B-cells.

Applicant contends that the methods recited by new independent claim 50 and claims 51-54 which depends therefrom, are also supported by the as-filed specification. More specifically, the specification describes several methods of detecting transporter peptide translocation such as biochemical, immunohistochemical and fluorescent labeling. First, the specification discloses a biochemical method of detection wherein B-cells incubated with phage-bearing peptides were removed, the B-cells were harvested and lysed to release the internalized phages, and the transporter peptides displayed by the internalized phages were sequenced. (*See* specification at

pg. 21, lines 24-27) This method was used to detect the transporter peptides having the sequence $X_mRX_oRX_n$. Specifically, transporter peptides with SEQ ID NOs: 1, 2, 3 and 6 were detected.

Second, the specification describes an immunohistochemical method of detection wherein internalized phages displaying transporter peptides were visualized in B-cells by treating the B-cells with an antibody directed to the phage capsid and then treating the cells with a fluorescein-conjugated antibody directed to the first antibody allowing visualization of internalized phage-bearing peptides by fluorescence microscopy. (*See* specification at pg. 21, line 31 through pg. 22, line 4).

Finally, the specification discloses a method of detection whereby the transporter peptides are themselves fluorescently labeled for visualization by fluorescence microscopy (*See* specification at pg. 24 lines 15-20). More specifically, a transporter peptide of SEQ ID NO:1 was linked to a 10-amino acid random sequence labeled with FITC. While the FITC-labeled transporter peptides were visualized in B-cells, the labeled transporter peptides were not visualized in other cell types. In light of the support in the specification, Applicant contends that the specification as-filed supports new claims 50-54.

V. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner has rejected claim 14 under 35 U.S.C. §112, second paragraph as being indefinite. According to the Examiner, claim 14 fails to particularly point out and distinctly claim the subject matter regarded as the invention. Applicant notes claim 14 has been amended herein to recite a method translocating a transporter peptide into a pancreatic B-cell by contacting with a transporter peptide under conditions sufficient to permit translocation of a B-cell membrane. Further, Applicant contends that claim 14 as amended is not indefinite because it contains clear terms supported by the specification. (*see, e.g.,* specification at pg. 21, lines 17-22)

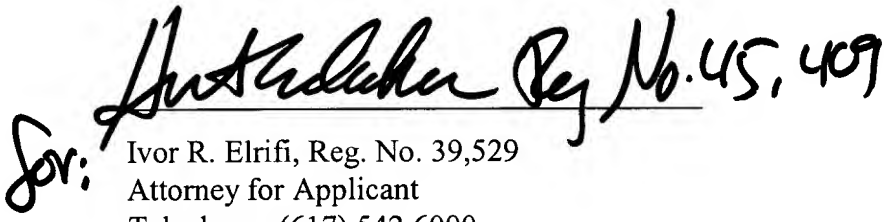
Second, the Examiner has rejected claim 14 under 35 U.S.C. §112, second paragraph as being incomplete for omitting essential steps. In particular, the Examiner has asserted that claim 14 does not recite how the transporter peptides are translocated across the membrane of pancreatic B-cells. As discussed above, claim 14 has been amended herein to recite the method steps for translocating a transporter peptide into a pancreatic B-cell. Applicant contends,

therefore, that the pending claims do not omit essential steps. As a result, Applicant requests the Examiner withdraw this rejection.

CONCLUSION

On the basis of the foregoing amendments, Applicant respectfully submits that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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